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Research Article

FORMULATION AND IN VITRO EVALUATION OF LOSARTAN POTASSIUM MUCOADHESIVE BUCCAL TABLETS

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ABSTRACT

Objective: The Losartan potassium mucoadhesive buccal tablet were prepared using mucoadhesive polymers such as Carbopol 940P, pectin, sodium CMC, Sodium alginate, HPMC K4M, HPMC K15M and HPMC K100M in alone and in combination as release retarding agent to prolong the drug release and to avoid first pass metabolism. **Methods:** The mucoadhesive buccal tablets were prepared by direct compression method. The prepared mucoadhesive buccal tablets were evaluated for physicochemical parameters such as hardness, thickness uniformity, weight variation, and surface pH and moisture absorption studies. The prepared buccal tablets were also evaluated for mucoadhesive strength, *ex-vivo* residence time, *in vitro* drug release and drug permeation through porcine buccal mucosa. The drug excipients compatability was evaluated by DSC studies. **Results:** *Ex vivo* mucoadhesive strength, *ex- vivo* residence time and *in vitro* release studies showed that formulation F10 containing 1:1.25 ratio of drug and polymer combination showed satisfactory bioadhesive and exhibited optimum drug release (91.33 % after 12hrs). DSC results showed no evidence of interaction between the Losartan potassium and mucoadhesive polymers. The results indicated that suitable bioadhesive buccal tablets with desired permeability could be prepared. The Stability of Losartan potassium mucoadhesive buccal tablets was determined in natural human saliva; it was found that both Losartan potassium and buccal tablets were stable in human saliva. **Conclusion:** Hence different mucoadhesive polymers (Carbopol 940P, pectin, Sodium CMC, Sodium alginate and HPMC different grades) in various proportions can be used to prepare mucoadhesive buccal tablets of Losartan potassium having prolonged therapeutic effect with enhanced patience compliance by avoiding first pass metabolism.

Keywords: Losartan potassium, mucoadhesive buccal tablets, HPMC K100, Carbopol 940P, Formulation, Evaluation

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming drawbacks associated with the oral mode of dosing [1-3].Buccal delivery involves the administration of active pharmaceutical ingredients (API) through buccal mucosa (the lining in the oral cavity) [4,5]. Problems such as first pass metabolism and drug degradation in the gastrointestinal tract acid environment can be circumvented by administering the drug via buccal route [6]. Moreover, the buccal cavity is easily accessible for self medication and drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity [7,8]. The API administered through buccal mucosa reaches to the systemic circulation through the internal jugular vein and bypasses the API from the hepatic first pass metabolism, which leads to high bioavailability [9]. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site [10]. In addition, there is excellent acceptability, an expanse of smooth muscle, immobile mucosa, less enzymatic activity, suitable for drugs that mildly and reversibly damage or irritate the mucosa [11, 12]. Buccal drug delivery system utilizes mucoadhesive polymers which become adhere to the buccal mucosa upon hydration and hence act as targeted or controlled /sustained release system [13]. Various mucoadhesive dosage forms suggested for oral drug delivery which include adhesive tablets, [14] adhesive patches [15], adhesive gels [16], strip [17], ointment [18] and discs [19].

Losartan potassium is an orally active non-peptide angiotensin-II receptor antagonist. It is the first of a new class of drug to be introduced for clinical use in "hypertension" due to selectively blockade of AT-1 receptors and consequent reduced pressure effect of angiotensin II [20, 21]. It belongs to class III, is soluble in acidic pH. Losartan potassium is having narrow therapeutic index, poor bio availability (25 to 35%) and short biological half life (1.5 2hrs) [22, 23].

Conventional tablets should be administered 3-4 times to maintain plasma drug concentration. Administration of Losartan potassium in a buccal drug delivery system would be more desirable for antihyper tensive effects by maintaining the Losartan plasma concentration well above the minimum effective concentration. Developing a sustai ned release drug delivery system like buccal tablet for Losartan potassium is desirable for an effective treatment of hypertension and is useful to reduce the dosage frequency to improve patient compliance [24. Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for Losartan potassium using different combination of polymers in order to avoid first pass metabolism and prolonged effect.

MATERIAL AND METHODS

Materials

Losartan potassium was a gift sample from Aurobindo Pharma Ltd, Hyderabad. HPMC K4M, K15M, K100M, Carbopol and other polymers were received as gift sample from Cadila Pharma, Ahmedabad, India. Talc and Magnesium Stearate from S.D. fine chem icals Pvt. Ltd.MCC was procured from Signet Chemicals. All other ingredients used were of analytical grade

Mucoadhesive buccal tablets preparation

Losartan potassium Mucoadhesive buccal tablets were prepared by direct compression technology. The formulations composition is shown in Table 1. All the powders passed through a 60 mesh sieve. The required quantity of drug, various polymer mixtures and diluent were mixed thoroughly in polybags. The blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant. The mixed blend was directly compressed (7mm diameter, round flat fac ed punches) using multiple punch tablet compression machine (Cad mach Ltd. India). Each tablet contained 50 mg of Losartan potassium . All the tablets were stored in airtight containers for further study.

Table 1: Composition of Losartan potassium buccal tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Pectin	50	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sodium alginate	-	50		-	-	-	-	12.5	25	25	25	-	-	-	-
Sodium CMC	-	-	50	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 940P	-	-	-	50	-	-	-	-	-	-	-	12.5	25	25	25
HPMC K4M	-	-	-	-	50		-	-	-	-	-	-	-	-	-
HPMC K15M	-		-	-	-	50	-	-	-	-	-	-	-	-	-
HPMC K100M	-		-	-	-	-	50	12.5	25	37.5	50	12.5	25	37.5	50
MCC	38	38	38	38	38	38	38	38	38	38	38	38	38	38	38
Aerosil	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total weight	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Evaluation of buccal tablets

Hardness

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage, depends on its hardness. The hardness of ten randomly selected Losartan potassium buccal tablets from each batch was measured using Monsanto Hardness tester (Secor Scientific Eng Corporation India) and expressed in Kg/cm^2. The mean and standard deviation values were calculated and reported.

Weight variation test

All prepared Losartan potassium buccal tablets were evaluated for weight variation as per USP monograph. Twenty tablets were randomly selected from each batch and individually weighed using an electronic balance. The average weight was calculated, individual tablet weight was then compared with the average value to find out the deviation in weight and percent variation of each tablet was calculated [25].

Friability

Roche friabilator was used to determine the friability by following procedure. Pre weighed 10 tablets from each batch were taken in Roche friabilator (Pharma labs, Ahmedabad, India) apparatus that revolves at 100 rpm for 4 minutes dropping the tablets through a distance of 6 inches with each revolution. At the end of test, tablets were reweighed and the percentage loss was determined.

Thickness

Ten randomly selected Losartan potassium buccal tablets from batch were used for thickness determination. Thickness of each tablet was measured in mm using a digital Vernier Caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan). The mean and standard deviation values were calculated and reported.

Drug content estimation

Twenty tablets from each formulation were weighed and grounded in a mortar with pestle to get fine powder. From the mixture quantity equivalent to 50mg of Losartan potassium was accurately weighed and extracted thoroughly with100 ml water by sonication for 30 min. The solution is filtered through Whatman filter paper the Losartan potassium content was analyzed spectrophotometrically at 250 nm using an UV spectrophotometer (Elico, India). Each reading was carried out in triplicate and the average Losartan content in the buccal tablet was calculated [26].

Determination of surface pH

The Surface pH of the prepared muco-adhesive Losartan potassium tablets was determined to evaluate the possible irritation effects on the mucosa. The Losartan potassium buccal tablets were placed in glass tubes and allowed to swell in contact with distilled water (12ml) and the pH was measured by bringing the pH paper, in contact with the surface of the tablet and allowing it to equilibrate for 1 min [27].

Moisture absorption study

Agar (5% w/v) was dissolved in hot water, transferred into Petri plates and allowed to solidify. Six Losartan potassium buccal tablets from each batch were placed in vacuum over night prior to the study to remove moisture if any and weighed initially, laminated on one side with cellophane tape (impermeable backing membrane). Then buccal tablets were placed on the surface of the agar and incubated at 37^{0}C for 1 hour. At the end of test, buccal tablets were reweighed and the percentage moisture absorption was calculated using the following formula [28].

$$\% \text{ Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

***In vitro* drug release study**

The Losartan release rate from buccal tablets was studied using the USP type II (paddle) dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane (cellophane tape) was placed one side of the tablet further tablets was fixed to a 2x2 cm glass slide with cyanoacrylate adhesive and immersed into dissolution media. The dissolution test was (Electrolab Pvt. Ltd., India) performed using 500 ml of distilled water, at 37 ± 0.5°C and 50 rpm. Five ml of samples were periodically withdrawn and replaced with an equal volume of fresh distilled water. The Samples were collected at different time intervals up to 12hrs and analyzed after suitable dilution at 250 nm using UV-Visible spectrophotometer (Elico, Ahemadabad, India) [29].

Release kinetic studies

To find out the mechanism of drug release from Losartan potassium buccal tablets, the *in vitro* release data was treated with different kinetic models, namely zero order, first order, Higuchi and Korsemeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value [30].

Ex-vivo mucoadhesive strength

Ex vivo mucoadhesive strength of Losartan potassium buccal tablets was measured by using modified physical balance method .Fresh porcine buccal membrane was obtained from male/female pigs with an average weight of 65 ± 6 kg, from the local slaughterhouse and stored in phosphate buffer pH7.4 and the experiment was performed within 3 h of procurement of pig mucosa. The porcine buccal mucosa was fixed to the stainless steel piece with a cyanoacrylate adhesive and placed in a beaker; then pH 7.4 phosphate buffer was added into the beaker up to the upper surface of the porcine buccal mucosa to maintain buccal mucosal viability during the experiment. Then the tablet was attached to the upper clamp of the apparatus and the beaker was raised slowly to establish contact between porcine buccal mucosa and the Losartan potassium buccal tablet. A preload of 50 gm was placed on the clamp for 5 mins to establish adhesive bond between the buccal tablet and porcine buccal mucosa. After completion of preload time, preload was

removed from the clamp and water was added into the beaker from burette at a constant rate. The weight required to detach the buccal

tablet from the mucosal surface gave the measure of mucoadhesive strength in gm (total weight of water in beaker). Experiments were carried out triplicate and the average values were recorded [31].

***Ex vivo* residence time**

The *Ex vivo* residence time for Losartan potassium mucoadhesive buccal tablets was determined using a modified USP dissolution apparatus. The dissolution medium was composed of 500 ml of phosphate buffer pH 7.4 maintained at 37°C. A segment of porcine buccal mucosa each of 3 cm length was glued to the surface of glass slab which was then vertically attached to the apparatus. Three adhesive tablet each batch were hydrated using 15µl of pH 7.4 buffer on one side and hydrated surface was brought into contact with mucosal membrane for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing phosphate buffer pH 7.4. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time necessary for complete erosion or detachment of the Losartan potassium buccal tablet from the mucosal surface was recorded [32].

***Ex vivo* permeation studies**

Ex vivo permeation study of Losartan potassium mucoadhesive buccal tablet was carried out on porcine buccal membrane using modified Franz diffusion cell with a diffusion area of 17.35 cm^2 and the acceptor compartment volume of 22 ml. A semi permeable membrane (porcine buccal membrane was clamped between the donor and acceptor compartments. The water in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer and maintained at 37 ± 5°C. The buccal tablet was placed into the donor compartment and was wetted with 1ml of water. The diffusion was carried out for 8 h. The amount of Losartan potassium permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of water. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically (Elico, India) at 250 nm [33].

DSC Studies

The DSC analysis of pure drug, drug+ Sodium alginate & HPMC K100M, drug+ HPMC K100M & Carbopol 940P, were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. Accurately weighed 5-6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10°C/min over a temperature range of 40 to 300 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

Stability of buccal tablets

Stability studies of Losartan potassium mucoadhesive buccal tablets were performed for best formulation F10 in normal human saliva. The human saliva was collected from human healthy volunteers (aged 24 years) and filtered through filter paper. Losartan potassium buccal tablets were immersed in separate petri dishes containing 5 mL of human saliva and placed in a temperature-controlled oven for 6 hr at 37°C ± 0.2°C. At predetermined time interval the Losartan potassium buccal tablets were evaluated by observing change in color, shape, collapse of the tablet and change in pH. The experiments were repeated in triplicate (n = 6) [34].

RESULTS AND DISCUSSION

All the losartan buccal tablets with different proportion of polymer composition were within the weight range of 149.06 ± 0.75 mg to 150.09 ± 1.04 mg .The tablets thickness of the various formulations was found to be in the range of 3.52 ± 0.13 to 4.52 ± 0.32 (Table 2). The mass and thickness of all compressed tablets were within the limit as per USP. The hardness of tablets was optimized on the basis of trail preparation of tablets. The hardness of all prepared tablet were in the range of 5 to 6 kg/cm^2.Hardness increased as the amount of concentration of the polymers increased. The friability of all tablets was less than 1% i.e., in the range of 0.67– 0.88 % which is in the acceptable limits which indicates formulations have good mechanical strength.

Table 2: Physico chemical properties of Losartan potassium buccal tablets

Formulation code	Thickness (mm)	Friability	Weight variation	% Drug content
F1	3.69 ± 0.06	0.70	149.51± 0.87	99.13 ± 0.87
F2	3.65 ± 0.05	0.76	149.24± 0.82	100.43± 0.43
F3	3.78 ± 0.11	0.67	150.09± 1.04	99.56 ± 1.30
F4	3.81 ± 0.12	0.72	149.61 ± 0.86	100.02±0.44
F5	3.76 ± 0.05	0.88	149.95 ± 0.94	99.74 ± 1.26
F6	3.83 ± 0.13	0.82	149.40± 0.73	98.56± 0.50
F7	3.81 ± 0.11	0.69	148.86± 0.57	99.85 ± 0.66
F8	3.81 ± 0.11	0.86	149.27± 0.83	100.28± 0.66
F9	4.52 ± 0.32	0.83	148.58± 0.51	99.17± 0.82
F10	3.73 ± 0.05	0.69	149.90± 0.93	99.56 ± 0.44
F11	4.03 ± 0.16	0.80	150.09± 1.04	100.43±0.43
F12	3.60 ± 0.05	0.76	149.06± 0.75	99.85 ± 0.90
F13	3.67 ± 0.04	0.82	149.87± 0.93	100.02± 0.44
F14	3.93 ± 0.11	0.77	150.01± 1.01	99.02 ± 0.86
F15	3.52 ± 0.13	0.81	150.06±1.03	100.28± 0.66

The content uniformity of the entire formulations (F1 to F15) was evaluated and the results are presented in Table 2.The drug content in various formulations varied between 98.56±0.50 percent to 100.28± 0.66 %. The low values in standard deviation indicate uniform drug content in all the formulations.

In order to evaluate different charge bioadhesive polymers to prepare buccal tablets, seven different polymers i.e. Pectin, sodium alginate, sodium CMC, Carbopol 940, HPMC K4,HPMC K15,HPMC K100M were selected and dosage forms were prepared and their individual drug release profile were evaluated. It is observed that the type of polymers influences the drug release patterns as shown in fig.1.1-1.3. In anionic polymers formulation F1 and F3 containing pectin and sodium CMC retard drug release i.e 26.06 % and 46.78 % after 8 hour study. However formulation F2 exhibited the maximum drug release i.e. 86.04% after 8 hour study. In non ionic polymers the initial burst effect for the formulation F5 and F6 containing HPMC K4 and HPMC K15 was found to be more or high. However

that the formulation F7 contains HPMC K100M was found to retard the drug release more than 8 hours. Considering the drug release patterns, Sodium alginate, HPMC K100M and Carbopol were used in combination for further study.

Formulations F8 released the drug completely within 8 hours; F9 released the drug completely within 10hrs, whereas formulation F10 and F11 retarded drug release beyond 12 hours. Formulations F12 released the drug completely within 9 hours. The drug release was extended beyond 12 hours in formulations F13 to F15. *In vitro* drug release studies revealed that the release of Losartan potassium from different formulations varied according to the type and ratios of the matrix forming mucoadhesive polymers. The possible reason for

observed reduction in total drug release may be the interaction between two charged bioadhesive polymers i.e Sodium alginate (anionic) and HPMC K100M M (non ionic) in formulations F8 to F11, Sodium alginate (anionic) and Carbopol 940 (anionic) in formulation F12 to F15 .

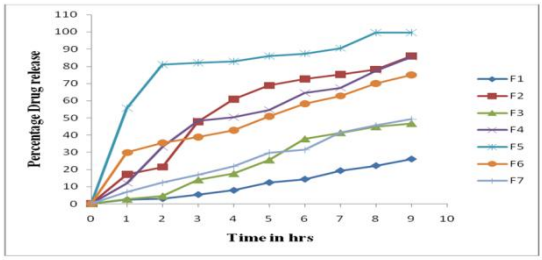

Figure1.1: Comparative release profile of formulation F1 to F7

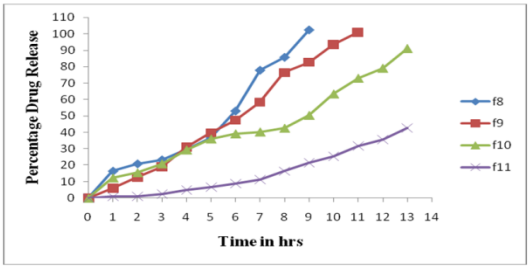

Figure1.2: Comparative release profile of formulation F8 to F11

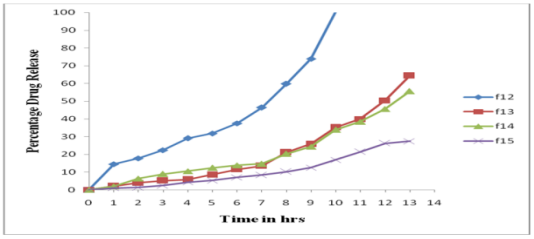

Figure1.3: Comparative release profile of formulation F12 to F15

In-vitro drug release data of formulations F8 to F15 were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release (Table 3).In case of F10 formulation the r^2 value indicated that the highest r2 (0.966) value was found for zero order. According to n value it is between 0.5-1, so it follows non-fickian diffusion with zero order release.

The values of the mucoadhesive strength of Losartan potassium mucoadhesive buccal tablets are given in table 4. The mucoadhesive strength were influenced by the nature and proportions of the mucoadhesive polymers used in the formulations .In all the formulations, as the mucoadhesive polymer mixture concentration increased, the mucoadhesive strength also increased. The order of mucoadhesive strength of bioadhesive polymers used in the formulations can be given as carbopol 940 > sodium alginate > pectin > HPMC K100M > HPMC K15M > sodium CMC > HPMC K4M. Buccal tablets formulated with a mixture of carbopol 940 and HPMC K100M showed comparatively higher bioadhesion than that of sodium alginate and HPMC K100M.Very strong mucoadhesion could damage the epithelial lining of the buccal mucosa. Mucoadhesive strength exhibited by the formulation F10 tablets can be considered satisfactory for maintaining them in the oral cavity for 12hrs. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity. The surface pH of the buccal tablets depends on the nature and composition of mucoadhesive polymers.

Surface pH of the all the formulation were found to be in the range of 6.5 to 7.0. This pH is near to the neutral, so the buccal tablet does not cause any irritation on the mucosa.

Moisture absorption studies give an indication of the relative moisture absorption capacities of mucoadhesive polymer mixtures and whether the formulations maintained their integrity after its absorption. Moisture absorption was increased from formulation F8 to F11 and F12 to F15.The hygroscopic nature of the polymers is one of the important property that affecting moisture absorption. The increasing moisture absorption of formulations may be due to the increased concentration of polymer mixture from formulation F8 to F11 and F12 to F15.The moisture absorption was more in formulations containing carbopol 940 and HPMC K100M group when compared to formulation containing sodium alginate and HPMCK100M (Table 4). This may be due to the more hydrophilic nature of carbopol. Among all the formulations the F10 formulation showed minimum matrix erosion and optimum moisture absorption 36.83±0.04% at the end of 8 hrs.

Table 3: Kinetic parameters of Losartan potassium buccal tablets

Formulation code	Zero order	First order	Higuchi	Korsemyer pepas	n-value	Hixoncrowel
F8	0.954	0.886	0.852	0.53	0.52	0.748
F9	0.999	0.884	0.92	0.787	0.19	0.824
F10	0.966	0.802	0.906	0.626	0.7	0.829
F11	0.946	0.913	0.793	0.967	0.75	0.859
F12	0.921	0.973	0.817	0.528	0.58	0.82
F13	0.899	0.814	0.735	0.892	0.76	0.829
F14	0.924	0.865	0.792	0.624	0.24	0.829
F15	0.937	0.885	0.791	0.958	0.86	0.845

Table 4: Physico chemical properties of Losartan potassium buccal tablets

Formulation code	Moisture absorption	Mucoadhesive strength (gm)	Ex vivo residence Time (hrs)
F1	15.41± 0.03	11.65± 0.08	6 hr 30 min
F2	38.4 ± 0.03	12.07± 0.08	4 hr 15 min
F3	35.69 ±0.02	10.99± 0.08	7 hr 45 min
F4	11.79± 0.03	14.53± 0.08	6 hr 30 min
F5	38.48±0.02	10.73± 0.08	2 hr 45 min
F6	12.49±0.04	11.34± 0.05	6 hr 15 min
F7	17.61±0.02	11.60± 0.05	7 hr 30 min
F8	30.77± 0.01	10.33± 0.04	7 hr 15 min
F9	35.70±0.02	27.99± 0.07	7 hr 45 min
F10	36.83±0.04	35.10±0.08	Above 8 hrs
F11	53.80± 0.04	38.45± 0.05	Above 8 hrs
F12	42.05± 0.05	26.82± 0.07	6 hr 45 min
F13	43.79± 0.03	28.56± 0.07	7 hr 30 min
F14	46.57±0.02	30.01± 0.04	Above 8 hrs
F15	50.14± 0.14	32.91± 0.05	Above 8 hrs

The *Ex vivo* residence time was determined by using modified physical balance method. Formulations F8 to F11 showed lower residence time when compared to the formulations F12 to F15 (Tabl e 4 & figure 2). As the concentration of mucoadhesive polymer incre ased in formulations, the residence time also increased. This test reflectsthe mucoadhesive capacity of polymers used in formulations. The results revealed that the mixture of carbopol 940 and HPMC K 100M containing formulations showed better bioadhesion than the mixture of sodium alginate and HPMC K100M formulations

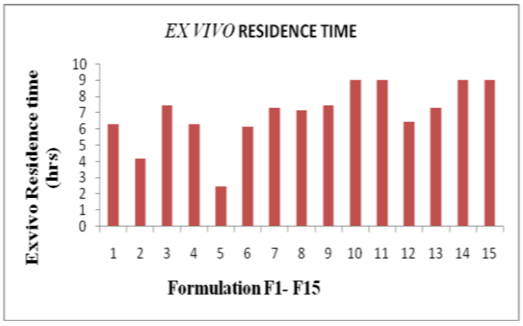

Figure 2: *Ex vivo* residence time of formulation F1 to F15

Based on ex *vivo* mucoadhesion, *ex vivo* residence time and in-*vitro* release studies formulation F10 was selected for *ex vivo* permeation study. Pigs resemble that of humans more closely than any other animal in terms of structure and composition and therefore porcine buccal mucosa was selected for Losartan potassium Permeation studies.

The results of drug permeation from Losartan potassium buccal tablets through the porcine buccal mucosa revealed that Losartan was released from the tablet and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady (fig 3) and 31.56 % of Losartan could permeated through the buccal membrane in 8 hours.

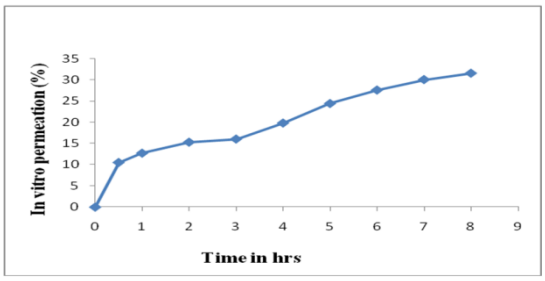

Figure 3: *In vitro* permeation study of formulation F10

The stability studies performed in normal human saliva would be more accurate to mimic the stability of the Losartan potassium mucoadhesive buccal tablet in oral cavity *in vivo*. Based on the results of *ex vivo* mucoadhesion, *in-vitro* release studies, *ex vivo* residence, formulation F10 was selected for stability study. Stability studies in normal human saliva showed no change in the color of Losartan potassium buccal tablets, which would have happened if drug was unstable in human saliva. Results reveal that the buccal tablets are having sufficient stability in the human saliva. The thickness and diameter of tablets slightly changed due to swelling of the polymers in human saliva but buccal tablets did not collapse till the end of studies confirming that the device strength was sufficient. The data were shown in table.5.

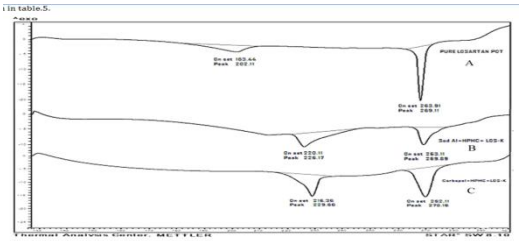

Figure4: DSC Thermograms of A. Pure Drug B.Formulation cont aining sodium alginate & HPMC K100 C. Formulation containing Carbopol 940P& HPMC K100

Table 5: Stability data of F10 formulation in human saliva

Time	Color change	Thickness (mm)	Change diameter shape (mm²)	Collapsing+
0	No change	3.73 ± 0.05	7.00 ± 0.01	No change
1	No change	3.79 ± 0.05	7.17 ± 0.01	No change
2	No change	3.91 ± 0.05	7.31 ± 0.01	No change
3	No change	4.13 ± 0.05	7.54 ± 0.01	No change
6	No change	4.24 ± 0.05	7.70 ± 0.01	No change

DSC studies were performed to investigate the physical state of Losartan potassium in the tablets and to know the interactions of drug with polymers in the formulations. Pure Losartan potassium showed a single sharp endothermic melting peak at 216.4º C (figure 4), which was unaltered in the thermogram of different polymer composition formulations evidencing the absence of interactions.

CONCLUSION

The overall results indicated that the polymers HPMC K100 and Sodium alginate in the ratio of 1: 1.25 showed satisfactory mucoadhesive properties. Among all the formulations, the F10 formulation using these polymers in the above ratio with drug exhibited significant bioadhesive properties with optimum release profile. The optimized formulation F10 also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability in human saliva. Hence it can be concluded that the formulation F10 will be useful for buccal administration of Losar tan .So, the mucoadhesive buccal tablets of Losartan potassium may be a good choice to bypass the hepatic first pass metabolism with an improvement in the bioavailability of Losartan potassium through B uccal mucosa.Further work is recommended to support its efficacy cl aims by pharmacodynamic and pharmacokinetic studies in human beings.

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REFERENCE

1. Wong CF, Yuen KH, Peh KK. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm 1999; 178: 11-22.
2. Gibaldi M. The number of drugs administering buccally increasing, Clinical Pharmacology. 1985; 3: 49-5.
3. Remunnan Lopez C, Portero A, Vila Jato JL, Alonso MJ. Design and evaluation of Chitosan / ethyl cellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release 1998; 55: 143-52.
4. Miller NS, Chittchang M, Johnston TP. The use of mucoadhesive polymers in buccal drug delivery. Adv Drug Del 2005; 57:1666–91.
5. S.Velmurugan, B.Deepika, K.Naga Raju .Formulation and *in vitro* evaluation of buccal tablets of Piroxicam. International Journal of ChemTech Research 2010; 2(3): 1958-1968.

6. John woodly. Bioadhesion; New Possibilities for Drug Administ ration; clinical pharmacokinetic 2001; 40(2): 77-84.
7. Wong, C.F., Yuen, K.H., Peh, K.K. Formulation and evaluation of controlled release Eudragit buccal patches. Int J Pharm 1999; 178, 11-22.
8. K.Naga Raju, S.Velmurugan, B.Deepika, Vinushitha. Formulation and In-Vitro Evaluation of Buccal Tablets of Metoprolol Tartrate.International Journal of Pharmacy and Pharmaceutical Sciences 2011; 3(2) : 239-246.
9. Gazzi Shaker, Chegonda Kumar, Chandra Sekhara Rao Gonugunta. Formulation and Evaluation of Bioadhesive Buccal Drug Delivery of Tizanidine Hydrochloride Tablets. AAPS PharmSci Tec 2009; 10(2): 530-539.
10. Remunnan-Lopez, C., Portero, A., Vila-Jato, J.L., Alonso, M.J. Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release 1998; 55:143-52.
11. Vamshi Vishnu Yamsani, Ramesh Gannu, Chandrasekhar Kolli,M. E. Bhanoji Rao and Madhusudan Rao Y. Development and in-vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm 2007; 57: 185-197.
12. Veuillez F, Kalia YN, Jaques Y, Deshusses J, Buri P. Factors and strategies for improving buccal absorption of peptides. Euro. J. Pharm. Biopharm 2001; 51: 93-109.
13. Nagai T, Machida Y, Buccal delivery systems using hydrogels, Adv. Drug Deliv. Rev 1993; 11: 179 -191.
14. Dortunc B, Ozer L, Uyanik N. Development and in vitro evaluation of a bucco adhesive pindolol tablet formulation. Drug Dev Ind Pharm 1998; 24:281-288.
15. Guo JH. Bioadhesive polymer buccal patches for buprenorphine controlled delivery: formulation in vitro adhesion and release properties. Drug Dev Ind Pharm 1994; 20:2809-2821.
16. Ishida M, Nambu N, Nagai T. Highly viscous gel ointment containing Carbopol for application to the oral mucosa. Chem Pharm Bull (Tokyo) 1983; 31:4561-4564.
17. Ilango R, Kavimani S, Mullaicharam AR, Jayakar B. In vitro studies on buccal strips of glibenclamide using Chitosan. Indian J Pharm Sci 1997; 59:232–235.
18. Bremecker KD, Strempel H, Klein G. Novel concept for a mucosal adhesive ointment. J Pharm Sci 1984; 73:548–552.
19. Yehia SA, El-Gazayerly ON, Basalious EB.Design and in vitro/in vivo evaluation of novel mucoadhesive buccal discs of an antifungal drug: relationship between swelling, erosion, and drug release. AAPS PharmSciTech 2008; 9(4):1207-17.
20. Brunton LL, Johns L, Parker KL. "Goodman & Gilman's.The Pharmacological Basis of Therapeutics 11th edition. Mc graw hil education pvt.ltd; New Delhi. 2006; 546-562.
21. Prajapati BG and Patel KR. Once-Daily Sustained-Release Matrix Tablets of Losartan potassium: Formulation and *In Vitro* Evaluation. Int J Medical and Clinical Res 2010; 1(1): 1-7.
22. Drug information for Losartan potassium from United States Pharmacopoeia, 2007, USP29-NF 24, page 1280.
23. Drug information for Losartan potassium from Indian Pharma copoeia.2010; 2: 1607-1608.
24. Rang and Dale, Hormones, Text Book of Pharamacology, 5th Edition, edited by Laurence Hunder, 2004.p. 385.
25. Gennaro A. (ed.) Remington: The Science and Practice of Pharmacy. 21th ed. Mack Publishing Company, Easton, 2006.p .917.
26. Bhanja satyabrata1, ellaiah p, mohanty chandan, k.v.r murthy, panigrahi bibhutibhusan and padhy sudhir kumar. Design and *in vitro* evaluation of mucoadhesive buccal tablets of perindopril Prepared by sintering technique. Asian J Pharm Clin Res 2010; 3(4): 4-10.
27. Brunella Cappello, Giuseppe De Rosa, Lucia Giannini, Maria Immacolata La Rotonda, Giuseppe Mensitieri, Agnese Miro, Fabiana Quaglia, Roberto Russo. Cyclodextrin-containing poly (ethyleneoxide) tablets for the delivery of poorly soluble drugs: Potential as buccal delivery system. Int. J. Pharm 2006; 319: 63– 70.
28. S.Velmurugan, B.Deepika, K.Nagaraju, Sundar Vinushitha. Formulation and in-vitro Evaluation of Buccal Tablets of Piroxicam. International Journal of PharmTech Research 2010; 2 (3): 1958-1968.
29. Rahul saxena, t.a.premchandani, r.c.saxena. Formulation and evaluation of buccoadhesive tablet of montelukast sodium. Asian J Pharm Clin Res 2011; 4(4): 65-68.
30. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52: 1145-1149.
31. Korsmeyer RW, Gunny R, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharmaceutics 1983; 15: 25-35.
32. Kashappa Goud H. Desai and T.M. Pramod Kumar. Preparation and Evaluation of a Novel Buccal Adhesive System, AAPS PharmSci Tech 2004; 5 (3) 35: 1-9.
33. Bhavin Patel, Piyush Patel, Ashok Bhosale and Shrawaree Hardikar**.** Evaluation of Tamarind Seed Polysaccharide (TSP) as a mucoadhesive and sustained release component of nifedipine buccoadhesive tablet & Comparison with HPMC and Na CMC. International Journal of PharmTech Research 2009; 1(3): 404-410.
34. Vamshi Vishnu Yamsani, Ramesh Gannu, Chandrasekhar Kolli, M. E. Bhanoji Rao and Madhusudan Rao Y. Development and *in vitro* evaluation of buccoadhesive carvedilol tablets. Acta Pharm 2007; 57: 185-197.